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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/566,063	01/26/2006	Alan Martin Birch	101159-1P US	2044

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EXAMINER	
RODRIGUEZ-GARCIA, VALERIE	
ART UNIT	PAPER NUMBER
1626	
MAIL DATE	DELIVERY MODE
10/16/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/566,063	BIRCH ET AL.	
	Examiner	Art Unit	
	VALERIE RODRIGUEZ-GARCIA	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5-10 and 16-23* is/are pending in the application.

4a) Of the above claim(s) *7-9,16-18 and 20-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3, 5, 6, 10 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

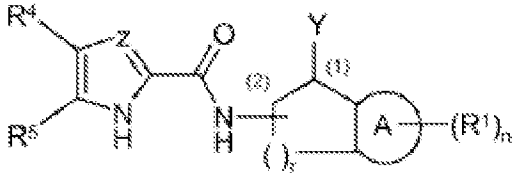
1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *05/19/06 and 05/19/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Claims 1, 3, 5-10 and 16-23 are currently pending. Claims 2, 4 and 11-15 have been canceled by applicant.

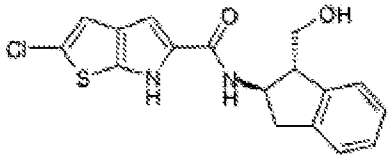
1. Applicant's election without traverse of Group I, claims 1-10 and 17-20 drawn to compounds of formula (1)



(1)

where Z= CH, r= 1 and A= phenylene, in the reply filed on 09/16/08 is acknowledged. The following elected species is also acknowledged:

Example 5: 2-Chloro-*N*-[(1*R*,2*R*)-1-(hydroxymethyl)-2,3-dihydro-1*H*-inden-2-yl]-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide



Subject matter not encompassed by elected Group I are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions there being no allowable generic or linking claim. Election was made without traverse in the reply filed on 09/16/08.

Priority

2. The current application is a 371 of PCT/GB04/03345 filed on 08/04/2004, which claims priority of application GB0318463.7 (08/07/2003).

Note

The species elected by the Applicant is free of the art. The search was extended to a next species.

Claims 7-9, 17-18 and 20 are withdrawn as being neither restricted to the elected species, nor reading on the species to which the search was extended.

Pursuant to Applicant's response, claims 1, 3, 5-10 and 16-23 are pending, claims 7-9, 16-18 and 20-23 are withdrawn, and claims 1, 3, 5, 6, 10 and 19 are treated on the merits in this action. This is the first Office Action on the merits of the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1, 3, 5, 6, 10 and 19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making the instantly claimed compounds, does not reasonably provide enablement for making or using pro-drugs and in-vivo hydrolysable esters thereof of the claimed compounds. The claims contain subject matter, which was not described in the specification in such a way as to enable one skilled in the art of medicinal chemistry to use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01 (A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the

existence of working examples, state of the art, predictability or unpredictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The instant claims recite a compound of formula (1) with many different variables, pro-drug and/or in-vivo hydrolysable esters thereof.

Breadth of the Claims: The instant claims include hundreds of thousands of compounds of formula (1) as recited in claim 1 as well as the presently unknown list of potential pro-drug derivatives and/or in-vivo hydrolysable esters thereof embraced by claims 1, 3, 5, 6, 10 and 19.

Guidance of the specification: The direction concerning the pro-drugs and in-vivo hydrolysable esters thereof is found in the instant specification (p.7, lines 18-33; p.8, lines 1-26).

State of the prior art: Wolff (Medicinal Chemistry) summarizes the state of the pro-drug art (Wolff, Manfred E. "Burger's Medicinal Chemistry, 5th Ed, Part I", John Wiley & Sons, 1995, pages 975-977). The table on the left side on page 976 outlines the research program to be undertaken to find a pro-drug. The second paragraph in section 10 and the paragraph spanning pages 976-977 indicate the low expectation of success. In that paragraph the difficulties of extrapolating between species are further developed. Since the pro-drug concept is a pharmacokinetic issue, the lack of any standard pharmacokinetic protocol discussed in the last sentence of this paragraph is particularly relevant. Banker et al. in the first sentence of third paragraph on page 596 states that

"extensive development must be undertaken" to find a pro-drug (Banker et al, "Modern Pharmaceutics, 3ed.", Marcel Dekker, New York, 1996, pages 451 and 596).

Existence of working examples/specification: There is no working example of a pro-drug of a compound represented by the formula (1).

The skill of those in the art: Wolff (Medicinal Chemistry) in the last paragraph on page 975 describes the artisans making Applicants' pro-drugs as a collaborative team of synthetic pharmaceutical chemists and metabolism experts. All would have a Ph. D. degree and several years of industrial experience.

The predictability or unpredictability of the art: It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

Amount of experimentation necessary: Finding a pro-drug is an empirical exercise. Predicting if a certain ester of a claimed compound, for example, is in fact a pro-drug, that produces the active compound metabolically in man at a therapeutic concentration and at a useful rate is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism *de novo*, this is still an experimental science. For a compound to be a pro-drug, it must meet three tests. It must itself be biologically inactive. It must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be clinically effective. Determining whether a particular compound meets these three criteria in a clinical trial setting requires a large quantity of experimentation.

MPEP 2164.01(a) states, "[a] conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to determine if any particular derivative is, in fact, a prodrug.

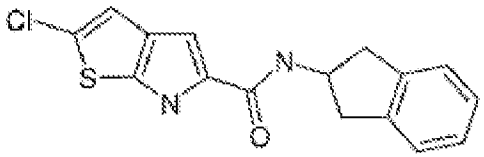
Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1, 3, 5, 6, 10 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 02/20530 A1 (cited in the international search report, IDS, and provided by applicant).

The instant claims are drawn to a compound of formula (I) where Z= CH, r= 1, A= phenylene and Y=1-4C alkyl. WO 02/20530 A1 discloses a compound of formula (I) where Z= CH, r= 1, A= phenylene and Y=H



. The prior art (p. 69, example 112) differs from the claimed invention only by a hydrogen on the Y position. Therefore, the difference between the prior art and the instant application is the presence of H versus methyl and longer alkyl chains.

It would have been obvious to those skilled in the chemical arts at the time the claimed invention was made to make and use analogs of the compounds of WO 02/20530 A1 to produce the instant invention. Analogs differing only in the substitution of hydrogen with methyl, are *prima facie* obvious, and require no secondary teaching. However, the examiner recalls *In Re Herr 134 USPQ 176.* It would be routine for the chemist to insert a methyl group in order to increase lipophilicity. The experienced chemist, who would make applicants' compounds, would be motivated to prepare these compounds on the expectation that structurally similar compounds would possess similar properties and because it is routine nature to perform such experimentation in the art of medicinal chemistry.

5. Claims 1, 3, 5, 6, 10 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 02/20530 A1 (cited in the international search report, IDS, and provided by applicant) in view of Wolff, M.E. *Burger's Medicinal Chemistry 4th Ed. Part I*, Wiley: New York, **1979**, 336-337.

Following the same reasoning above, to those skilled in the art, one homologue is not such an advance over adjacent member of series as requires

invention because chemists knowing properties of one member of series would in general know what to expect in adjacent members. *In re Henze*, 85 USPQ 261 (1950). The instant claimed compounds would have been obvious, because one skilled in the art would have been motivated to prepare homologues of the compounds taught in the reference with the expectation of obtaining compounds which could be used in pharmaceutical compositions. However, the examiner provides Burger's reference.

Wolff teaches that the addition of alkyl groups to active pharmacological agents often improves activity and bioavailability by increasing lipophilicity (see the examples in Table 8.2, p. 337 of a local anesthetic SAR). As such, it would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare compounds such as those of WO 02/20530 A1, with alkyl chains, as suggested by Wolff, to achieve better bioavailability.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to VALERIE RODRIGUEZ-GARCIA whose telephone number is (571)270-5865. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Joseph McKane can be reached on 571-270-0699. The fax phone number for the organization where this application or proceeding is

assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

VRG

/Kamal A Saeed, Ph.D./

Primary Examiner, Art Unit 1626